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Summary

Problem

Both military operations and civilian emergencies may require sustained work, entailing prolonged periods with little or no sleep. Under these conditions, stimulants, most commonly caffeine, often are used to try to maintain alertness. However, stimulants can interfere with subsequent sleep, decreasing sleep's recuperative effects on alertness and performance. Caffeine has been well documented to impair sleep, generally causing increases in sleep latency and wake time, with reductions in the deeper sleep stages. Situations where less than a full-night's sleep occurs prior to returning to work would make such sleep impairment particularly problematic.

Objective

The purpose of this study was to evaluate the effects of caffeine, administered in repeated doses during 64 hr of sleep deprivation, on alertness and performance during sleep deprivation and, in a subset of subjects, on subsequent nighttime recovery sleep. The focus of this report is caffeine effects on recovery sleep; effects on performance have been reported elsewhere.

Approach

Nocturnal polysomnography was performed before and after 64 hr without sleep. During the sleep deprivation, one group of subjects (n = 9) received 300 mg of caffeine every 6 hr (300-q6 group), one group (n = 11) received 400 mg of caffeine once each night (400-q24 hr group) and a placebo at the other 6-hr intervals, and the third group (n = 10) got a placebo every 6 hr (placebo group). Caffeine administration stopped 10.5 hr (300-q6 group) or 22.5 hr (400-q24 group) before the recovery sleep.

Results

Caffeine only affected sleep during the first third of the recovery night. Compared to baseline-night sleep, greater decreases occurred in Stage 2 sleep and greater increases in slow wave sleep (SWS) among subjects who received a placebo. Attenuation of the decrease in latency to sustained sleep and increase in total first third of the recovery-night sleep with caffeine appear to be due to ceiling effects.

Conclusion

Repeated administration of caffeine during sleep deprivation, thus, does not appear to interfere with recovery sleep deprivation, thus, does not appear to interfere with recovery sleep and may make short sleeps deeper, if it is not ingested close to the sleep period. The increased SWS may have resulted from caffeine withdrawal superimposed on up-regulated adenosine receptors, secondary to caffeine blockade of those receptors, and sleep deprivation.

Introduction

Both military operations and civilian emergencies may require sustained work, entailing prolonged periods with little or no sleep. Under these conditions, stimulants, most commonly caffeine, often are used to try to maintain alertness. However, stimulants can interfere with subsequent sleep, decreasing sleep's recuperative effects on alertness and performance. Caffeine has been well documented to impair sleep, generally causing increases in sleep latency and wake time, with reductions in the deeper sleep stages (1-5). Situations where less than a full-night's sleep occurs prior to returning to work would make such sleep impairment particularly problematic.

Most studies of caffeine effects on sleep have involved administration close to the sleep period, but in two studies sleep was recorded at least 7 hr after caffeine administration. Muehlbach and Walsh (6) reported that caffeine taken during simulated night work had no effect on total sleep time (TST), sleep latency, or sleep stages during subsequent daytime sleep periods (starting about 8 hr after the second nightly caffeine administration), compared with sleep in subjects who received a placebo. Landolt et al. (4) found reduced TST and EEG power density changes, suggesting decreased sleep depth during a sleep period that started at 2300, after administration of 200 mg of caffeine at 1710, but the reduction in slow wave sleep (SWS), as quantified by traditional hand scoring, was not significant.

Studies of caffeine effects on sleep rarely have involved sleep deprivation. LeBlanc et al. (5) studied 7 subjects during and after 48 hr of sustained operations (SUSOPS) followed by daytime recovery sleep. TST and amount of rapid eye movement (REM) sleep during recovery sleep were the same regardless of whether the subject had received caffeine (3 mg/kg every 4 hr) during the SUSOPS. Other sleep stages were not discussed.

We have found no reports on the effect of caffeine on nighttime recovery sleep following prolonged sleep deprivation. The purpose of this study, therefore, was to evaluate the effects of caffeine, administered in repeated doses during 64 hr of sleep deprivation, on alertness and performance during sleep deprivation and, in a subset of subjects, on subsequent nighttime recovery sleep. The focus of this report is caffeine effects on recovery sleep; effects of performance have been reported elsewhere (7).

Subjects and Methods

This double-blind, parallel-group study following the schedule outlined in Figure 1.

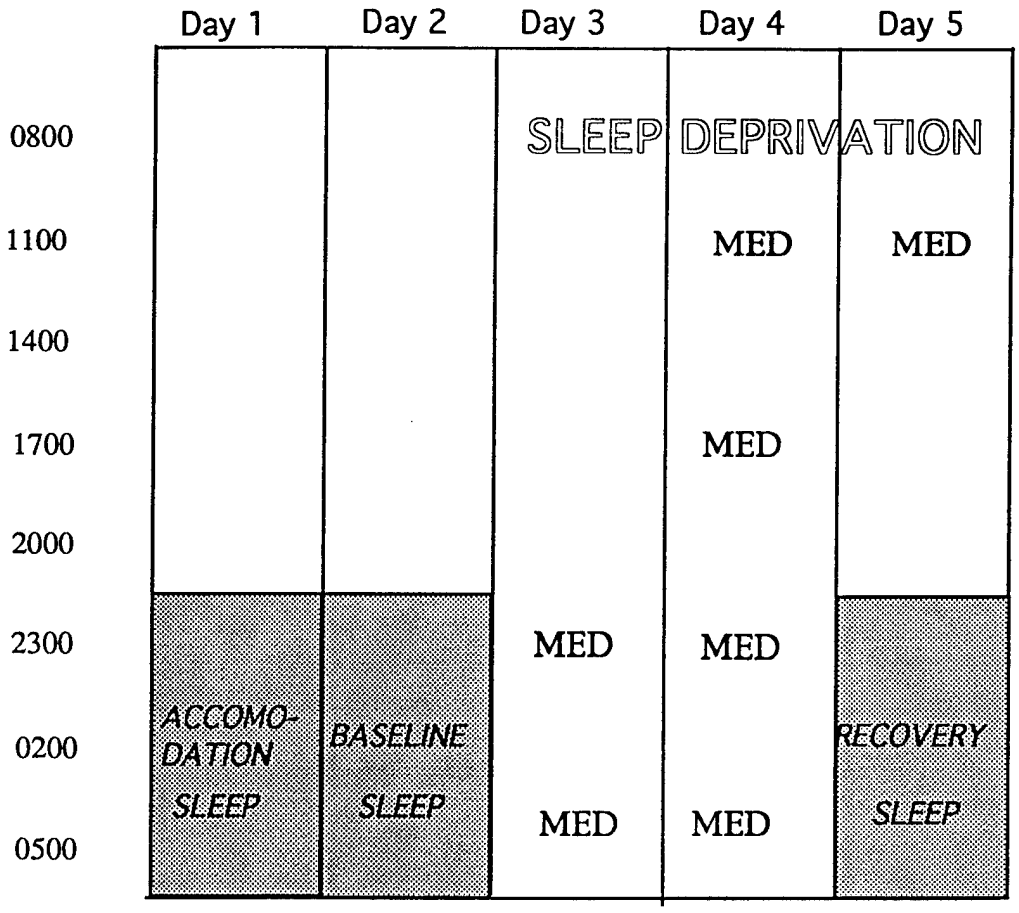


Figure 1. Study Schedule. MED = caffeine/placebo administration

Subjects were healthy, nonsmoking men who ordinarily consumed low to moderate amounts of caffeine (no more than 250 mg per day, based on a questionnaire). No subjects were totally caffeine naive. Sunday night an unrecorded accommodation sleep occurred in the laboratory. On the following day (Fig. 1, Day 2), they were trained on several tasks (7). That night, standard 8-hr sleep recordings, including EEG, EOG, EMG, and EKG, were performed. Subjects were awakened at 0600 on Day 3 to commence a 64-hr period without sleep, during which they received repeated cognitive testing. Between testing sessions, the subjects read, watched TV, or engaged in other sedentary activities, but they were not allowed to exercise. Four meals a day were provided. The subjects were constantly supervised to prevent them from sleeping.

Each subject took a capsule every 6 hr, starting at 2320 on Day 3 (7 capsules total). One group (n = 9, age = 19.7 ± 1.8 years) received 300 mg of caffeine each time (300-q6 group); one group (n = 11, age = 19.5 ± 1.4 years) received 400 mg of caffeine at 2320 each night and a placebo at other times (400-q24 group); and a third group (n = 10, age - 20.3 ± 2.1 years) received a placebo each time (placebo group).[a] After completion of the sleep deprivation period, an 8-hr recovery sleep with full polysomnography occurred during the night of Day 5.

Saliva samples were collected at baseline (morning of Day 3), 30 min after each caffeine or placebo administration, and the morning after the recovery sleep. These samples were assayed for caffeine content. The details of the assay have been reported elsewhere (8).

A single technician scored sleep records using standard scoring (9). The sleep measures were TST, latency to first sleep (SL), latency to 10 min of continuous sleep (SL10), REM latency (REML), Stage 1 sleep (S1), Stage 2 sleep (S2), SWS, and REM. TST and sleep stage data also were broken into third-of-the-night segments, as is standard for clinical sleep recordings.

Difference scores were calculated by subtracting the baseline-night value for each variable from the recovery-night value. One-way ANOVAs across the three drug groups were performed on the overall-night sleep data, and two-way ANOVAs (Group X Third) were performed on the third-of-the-night data. Tukey's HSD post-hoc multiple-range tests and t-tests were done as appropriate.

[a] One 300-q6 subject and 5 placebo subjects were excluded due to missing sleep data. One 300-q6 subject and one 400-q24 subject were excluded because salivary caffeine levels indicated they had not taken the caffeine consistently. The numbers reflect group sizes after subjects were excluded.

Results

Sleep Data

Overall-night baseline and recovery data and statistical comparisons are shown in Table 1. The ANOVA showed a Group effect for SL10, with the 300-q6 caffeine group showing less of a decrease in SL10 (2.3 ± 4.8 min) than the placebo group showed an intermediate decrease (11.2 ± 9.6 min), and the combined caffeine groups (CAFFEINE in Table 1) showed significantly less of a decrease in SL10 (7.2 ± 8.9 min) than did the placebo group.

Table 1.--Overall Night Sleep Measures in Minutes and Statistical Findings

	BASELINE NIGHT Mean(SD)			RECOVERY NIGHT Mean(SD)			GROUP EFFECT[1]		DIFFERENCE-SCORE COMPARISON TO PLACEBO GROUP[2]	
	PLACEBO	300-q6	400-q24	PLACEBO	300-q6	400-q24	F(2,27)	P	GROUP	P
SL	12(11)	7(3)	11(8)	4(4)	3(2)	2(1)	0.16	.95	----	----
SL10	24(18)	8(3)	13(10)	4(4)	6(5)	2(1)	5.66	.01	300-q6 CAFFEINE	.05 .05
REML	130(65)	78(20)	88(41)	86(56)	129(98)	105(90)	3.69	.04	300-q6 CAFFEINE	.05 .02
TST	443(13)	453(13)	445(12)	466(5)	461(13)	467(8)	2.49	.10	----	----
S1	25(19)	24(18)	26(13)	6(7)	7(6)	8(7)	0.27	.77	----	----
S2	261(43)	255(51)	238(28)	255(40)	232(41)	230(37)	0.35	.71	----	----
SWS	76(33)	82(38)	78(29)	126(48)	145(40)	144(43)	0.67	.52	----	----
REM	81(22)	92(19)	103(17)	79(23)	77(18)	86(29)	1.52	.24	----	----

[1] The ANOVAs were done on recovery minus baseline difference scores.

[2] CAFFEINE = combined caffeine groups. Tukey's HSD multiple-range test was used for 3-group comparisons. T-tests were used for comparisons between the combined caffeine groups and the placebo group.

REML also showed a Group effect: placebo subjects had shorter latencies to REM sleep on the recovery night as compared with the baseline night, while both caffeine groups had increased REML, with the 300-q6 group differing significantly from the placebo group. However, two subjects were extreme outliers for this measure, one placebo subject at baseline and one 300-q6 subject during the recovery night. When these subjects were excluded, the Group effect became only a trend ($p = .09$) and individual group comparisons were not significant; but when the two caffeine groups were combined, the change in REML (an increase of 32.3 ± 83.5 min) differed significantly ($p = .03$) form that in the placebo subjects (a decrease of 43.6 ± 62.8 min). No caffeine effects on sleep stages were found for the overall-night data.

Table 2 shows third-of-the-night data and the statistical comparisons. Significant Group X Third interactions occurred for TST and S2 and trends were seen for similar interactions for SWS and REM. Analyses of individual thirds of the night showed significant findings only for the first third of the night, for which there were Group effects on TST, S2 and SWS, with a trend for REM. Group comparisons showed that the 300-q6 group had significantly less of an increase in TST (5.9 ± 8.5 min) than did the placebo group (18.2 ± 11.8). This group also showed a decrease in REM of 9.6 ± 11.6 min, while the placebo group showed an increase of 7.3 ± 13.2 min. The 400-q24 group showed intermediate values for these variables and had more of a decrease in S2 (24.7 ± 23.0 min) and more of an increase in SWS (46.6 ± 12.9 min) than did the placebo group (4.81 ± 13.6 min and 23.3 ± 17.9 min, respectively).

Table 2.--Third-of-the-Night Sleep Measures in Minutes and Statistical Findings

		BASELINE NIGHT Mean(SD)			RECOVERY NIGHT Mean(SD)			GROUP X THIRD EFFECT[1]		FIRST-THIRD GROUP EFFECT[1]		DIFFERENCE-SCORE COMPARISONS TO PLACEBO GROUP[2]	
		PLACEBO	300-q6	400-q24	PLACEBO	300-q6	400-q24	F(4,54)	p	F(2,27)	p	GROUP	p
TST	1	137(14)	148(7)	143(7)	155(3)	154(5)	157(1)	2.44	.05	4.23	.03	300-q6	.05
	2	153(4)	152(6)	150(7)	156(3)	157(2)	155(5)					CAFFEINE	.05
	3	153(6)	153(7)	153(5)	155(2)	150(11)	156(4)						
S1	1	10(8)	7(7)	9(9)	3(3)	3(2)	2(2)	1.93	.45	0.76	.48	----	----
	2	7(8)	8(6)	7(5)	1(1)	1(1)	3(4)						
	3	7(5)	9(7)	10(6)	2(3)	3(4)	3(3)						
S2	1	68(16)	68(25)	66(15)	64(22)	47(15)	41(23)	4.62	.003	3.46	.05	400-q24	.05
	2	88(26)	89(13)	89(10)	89(23)	101(20)	92(15)					CAFFEINE	.02
	3	104(13)	97(22)	83(15)	102(12)	84(17)	96(14)						
SWS	1	49(23)	58(19)	48(22)	72(24)	98(16)	94(22)	2.17	.09	6.85	.004	400-q24	.05
	2	24(13)	17(14)	21(19)	42(21)	33(18)	34(17)					CAFFEINE	.001
	3	3(6)	7(10)	9(14)	13(11)	14(13)	15(14)						
REM	1	9(11)	15(9)	20(16)	16(14)	6(8)	19(23)	2.30	.07	3.17	.06	300-q6	.05
	2	33(10)	38(15)	32(16)	25(12)	22(12)	26(14)					CAFFEINE	.04
	3	39(13)	39(14)	51(7)	38(16)	49(11)	41(12)						

[1] The ANOVAs were done on recovery minus baseline difference scores.

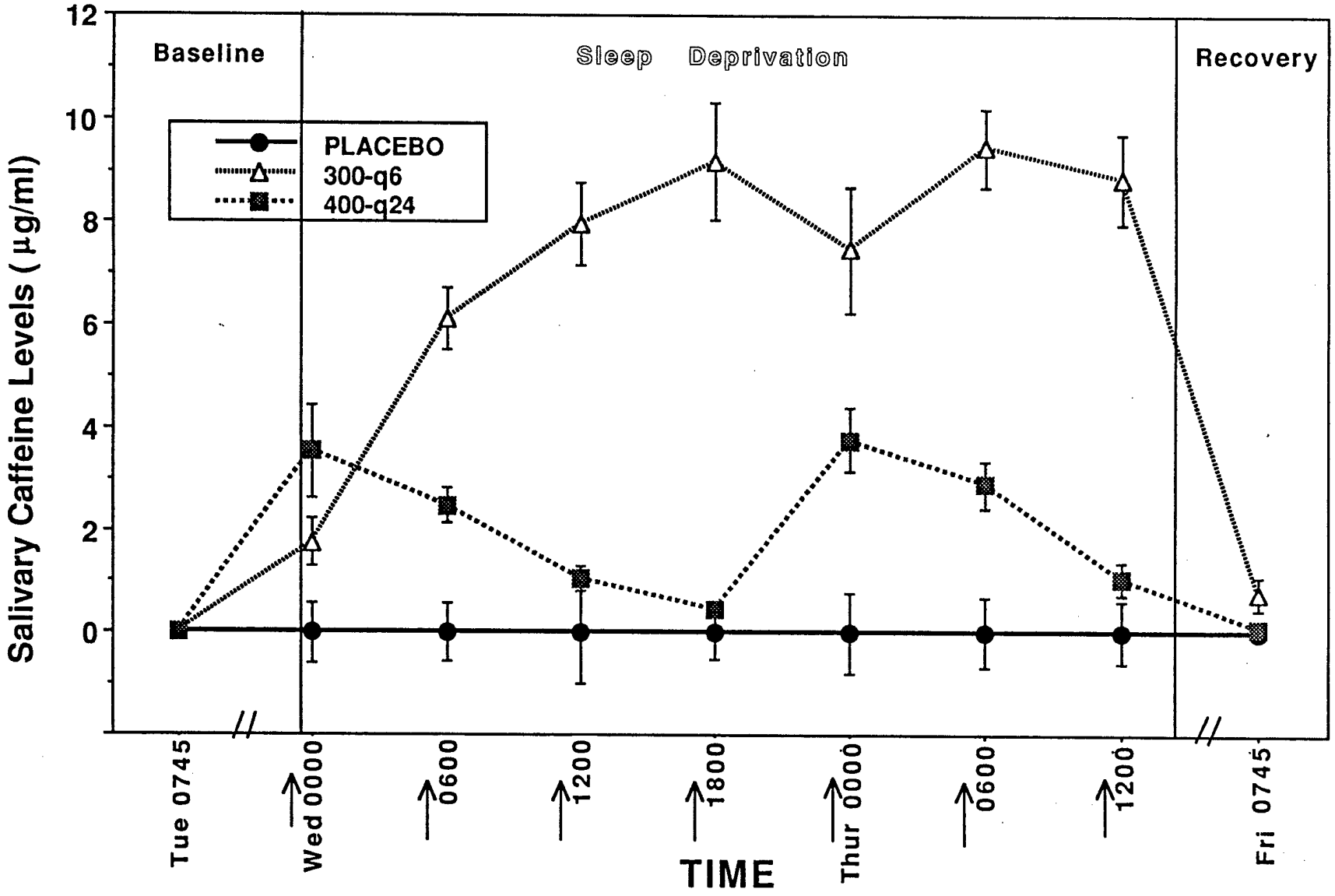
[2] CAFFEINE = combined caffeine groups. Tukey's HSP multiple-range test was used for 3-group comparisons. T-tests were used for comparisons between the combined caffeine groups and the placebo group.

The 300-q6 group showed intermediate values for SWS and S2. The combined caffeine groups (CAFFEINE in Table 2), had a greater increase in SWS (43.6 ± 13.2 min), greater decreases in S2 (22.9 ± 19.6 min) and REM (4.6 ± 15.5 min), and less increase in TST (10.4 ± 8.7 min) than the placebo group did during the first third of the night.

Salivary Caffeine Levels

Figure 2 shows salivary caffeine levels. The placebo group had nonmeasurable caffeine levels throughout the study. The 300-q6 group showed accumulation to a relatively steady state after 3 doses. Caffeine levels in the 400-q24 group dropped to about half of their peak after 6 hr, and were halved again after 6 more hours, consistent with the reported half life of caffeine of about 6 hr (2).

Figure 2. Salivary caffeine levels. Arrows indicate times of caffeine/placebo administration.



Discussion

Caffeine administration during sleep deprivation, 300 mg every 6 hr or 400 mg every 24 hr, affected the first third of the recovery-night sleep. Relative to baseline, subjects given caffeine decreased SL10 less than did the placebo subjects. First third-of-the-night S2 and REM decreased more, SWS increased more, and TST increased less in the caffeine subjects than in the placebo group.

The SL10 and first third-of-the-night TST findings are questionable because of ceiling effects. Sleep latency cannot be less than zero, and maximum TST in one third of an 8-hr sleep period is limited to 160 min. All groups approached these limits after sleep deprivation. The recovery-night values did not differ by more than 2 min between groups for either SL10 or TST; the group differences were due to the caffeine groups' slightly shorter SL10 and longer first third-of-the-night TST at baseline.

The sleep-stage findings, however, cannot be explained by ceiling effects or baseline differences. Caffeine administration made first third-of-the-night recovery sleep deeper, with less S2 and REM and more SWS. This contrasts with previous studies of caffeine's effects on sleep, which typically have shown decreased SWS.

The 300-q6 subjects must have had fairly high caffeine levels at the start of the sleep period. Previous studies have shown that salivary caffeine assays provide accurate values that are proportional to caffeine levels in blood (10). In our data, the relative levels of caffeine in saliva after the first 300-mg and 400-mg doses and the pattern of accumulation with repeated doses in the 300-q6 group (Figure 2) correspond well to what would be expected in blood with these doses and administration schedules. The 400-q24 subjects would have cleared most or all of the caffeine by the start of the sleep. The 300-q6 subjects had a mean level of 8.4 μg/ml 10 hr before recovery sleep. Two 6-hr half-lives would have reduced this to 2.1 μg/ml, around the level after a single dose of 300 mg (about 3 cups of coffee). Thus, the 300-q6 subjects were expected to show decreased, not increased, SWS compared with the placebo group, particularly during the early part of the sleep period.

One possible explanation for the increased SWS is that caffeine increased body temperature, and the increased energy expenditure was equivalent to a longer period of sleep deprivation, thereby increasing SWS rebound. However, temperature was monitored with oral basal temperature thermometers at 3-hr intervals, and no differences occurred in mean body temperature between the groups during the drug administration period (97.86 ± .2°F, 97.86 ± .33°F, and 97.73 ± .39°F for the placebo, 300-q6, and 400-q24 groups, respectively).

Another possible explanation for the increased SWS relates to adenosine receptors. Caffeine blocks adenosine receptors, leading to up-regulation in the number of receptors (11). Receptor up-regulation is associated with an increase in some of the effects of adenosine (12-14). Adenosine has been reported to have a sedative effect (15), and to increase SWS (16). At the

start of the sleep period, the 400-q24 group had little or no caffeine remaining, and residual caffeine levels in the 300-q6 group were low compared with those present during the preceding 48 hr. Thus, unblocked, up-regulated adenosine receptors should have been present, with increased sensitivity to endogenous adenosine.

Fatigue is a major component of the caffeine withdrawal syndrome (17,18), which could imply that withdrawal would improve sleep. However, this has not been borne out in studies involving caffeine withdrawal. Bonnet and Arand (1) found no SWS or other sleep stage alterations during withdrawal from chronic caffeine administration compared with baseline sleep prior to caffeine administration, and similar findings occurred in the simulated night-shift-work study of Muehlbach and Walsh (6), which included a period of caffeine withdrawal. Only whole-night data were reported in these two studies, but there were similar findings for the first third-of-the-night data in the Bonnet and Arand study (unpublished observations). Since subjects in that study ingested as much as 250 mg of caffeine per day up to the day prior to their baseline study, it is possible that the baseline night represented withdrawal from chronic caffeine consumption as well; it takes more than 48 hr to reverse caffeine-related up-regulation of adenosine receptors (19). Nevertheless, subjects received 1200 mg of caffeine per day during the administration period, so adenosine receptor up-regulation should have been much higher than at baseline.

The difference in findings between the study of Bonnet and Arand (1) and our present study may indicate that caffeine withdrawal will increase SWS only in the context of sleep deprivation. The limitation of caffeine effects on sleep stages in the present study to the first third of the night, when sleep-deprivation effects must be strongest, also supports this theory.

The first third-of-the-night data further suggest that sleep during nighttime naps after sleep-deprivation will be deeper in subjects who are withdrawing from chronic caffeine consumption of more than a 24-hr duration than in subjects who have not consumed caffeine during the sleep deprivation. The minimal separation between caffeine and sleep that will allow this increase in SWS is uncertain. Based on our data, it will occur with a separation of 10-24 hr. It also remains to be determined whether the SWS increase would be seen in daytime naps.

Increased SWS could have particular relevance in SUSOPS. Appropriately timed use of caffeine during SUSOPS, which typically involve sleep deprivation, should not hurt sleep and might increase the restorative effect of relatively short (2-3 hr) naps by making sleep deeper. SWS is thought to have the greatest restorative value, although this has never been proved (20), and some evidence suggests different sleep stages provide equally restorative effects (21-23).

Increased SWS in naps could have an adverse effect as well. The increased likelihood of awakening out of SWS might augment the risk of severe sleep inertia ("sleep drunkenness"), with poor performance for some period after awakening. However, since SWS is highly likely during naps after sleep deprivation, even without caffeine, personnel should be protected from having to perform critical activities shortly after awakening.

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13. ABSTRACT *(Maximum 200 words)*

Both military operations and civilian emergencies may require sustained work, entailing prolonged periods with little or no sleep. Under these conditions, stimulants, most commonly caffeine, often are used to try to maintain alertness. However, stimulants can interfere with subsequent sleep, decreasing sleep's recuperative effects on alertness and performance. Caffeine has been well documented to impair sleep, generally causing increases in sleep latency and wake time, with reductions in the deeper sleep stages. Situations where less than a full-night's sleep occurs prior to returning to work would make such sleep impairment particularly problematic. The purpose of this study was to evaluate the effects of caffeine, administered in repeated doses during 64 hr of sleep deprivation, on alertness and performance during sleep deprivation and, in a subset of subjects, on subsequent nighttime recovery sleep. The focus of this report is caffeine effects on recovery sleep; effects on performance have been reported elsewhere. Nocturnal polysomnography was performed before and after 64 hr without sleep (continued next pg)

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13. ABSTRACT (cont)

During the sleep deprivation, one group of subjects (n=9) received 300 mg of caffeine every 6 hr (300-q6 group), one group (N=11) received 400 mg of caffeine once each night (400-q24 hr group), and a placebo at the other 6-hr intervals, and the third group (n=10) got a placebo every 6 hr (placebo group). Caffeine administration stopped 10.5 hr (300-q6 group) or 22.5 hr (400-q24 group) before the recovery sleep. Caffeine only affected sleep during the first third of the recovery night. Compared to baseline-night sleep, greater decreases occurred in Stage 2 sleep and greater increases in slow wave sleep (SWS) among subjects who received a placebo. Attenuation of the decrease in latency to sustained sleep and increase in total first third of the recovery-night sleep with caffeine appear to be due to ceiling effects. Repeated administration of caffeine during sleep deprivation, thus, does not appear to interfere with recovery sleep deprivation, thus, does not appear to interfere with recovery sleep and may make short sleeps deeper, if it is not ingested close to the sleep period. The increased SWS may have resulted from caffeine withdrawal superimposed on up-regulated adenosine receptors, secondary to caffeine blockade of those receptors, and sleep deprivation.

*Author does not work here any more, so we do not know.